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Health and Environmental Effects Profile for Temephos

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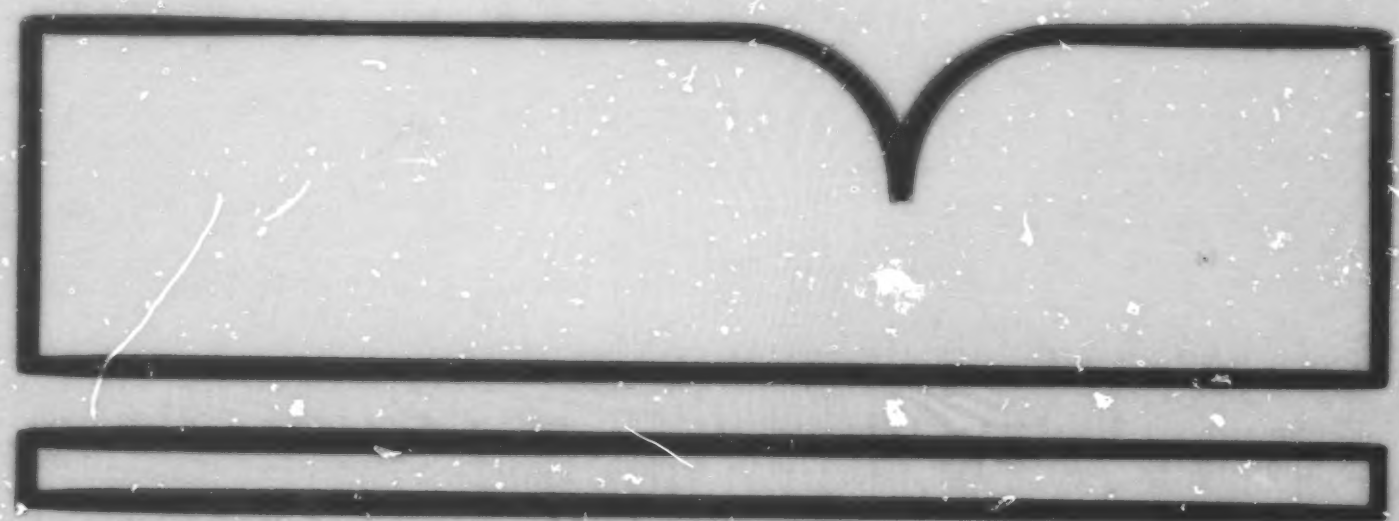

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR TEMEPHOS

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

The Health and Environmental Effects Profile for Temephos was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Temephos has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for Temephos is 5.4×10^{-3} (mg/kg bw/day) for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	2
2.	ENVIRONMENTAL FATE AND TRANSPORT	3
3.	EXPOSURE	7
4.	PHARMACOKINETICS	8
4.1.	ABSORPTION	8
4.2.	DISTRIBUTION	8
4.3.	METABOLISM	9
4.4.	ELIMINATION	9
5.	EFFECTS	11
5.1.	CARCINOGENICITY	11
5.2.	MUTAGENICITY	11
5.3.	TERATOGENICITY	11
5.4.	OTHER REPRODUCTIVE EFFECTS	12
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	12
5.6.	OTHER RELEVANT INFORMATION	16
6.	AQUATIC TOXICITY	18
6.1.	ACUTE TOXICITY	18
6.2.	CHRONIC EFFECTS	20
6.3.	PLANT EFFECTS	22
6.4.	RESIDUES	23
6.5.	OTHER RELEVANT INFORMATION	23
7.	EXISTING GUIDELINES AND STANDARDS	24
7.1.	HUMAN	24
7.2.	AQUATIC	24
8.	RISK ASSESSMENT	25
9.	REFERENCES	29
APPENDIX		40

LIST OF TABLES

No.	Title	Page
6-1	Acute Lethal Effects of Temephos to Freshwater Fish.	19
6-2	Acute Lethal Effects of Temephos to Aquatic Invertebrates. . .	21
8-1	Summary of Oral Sub-Chronic Studies on Temephos Toxicity to Laboratory Animals.	26

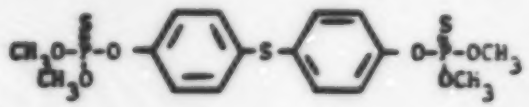
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
NOAEL	No-observed-adverse-effect-level
ppb	Parts per billion
ppm	Parts per million
RBC	Red blood cell
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Temephos is a synonym for phosphorothioic acid, O,O'-(thiodi-4,1-phenylene) O,O,O',O'-tetramethyl ester or phosphorothioic acid, O,O'-(thiodi-p-phenylene) O,O,O',O'-tetramethyl ester (U.S. EPA/NIH, 1983). This insecticide was introduced under the code number AC 52, 150 and trade names Abate, Abathion, Abat, Swebate, Nimitex and Biothion by American Cyanamid Company in 1965 (BCPC, 1977). Other common names include Bithion, Difenthos and Nimitox (NIOSH, 1983). The structure of temephos is shown below:



Molecular formula: $C_{16}H_{20}O_6P_2S_3$

Molecular weight: 466.4

The Chemical Abstracts Service (CAS) Registry Number for temephos is 3383-96-8.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

The technical product is a brown, viscous liquid, 90-95% pure. Pure temephos is a white crystaline solid (BCPC, 1977). Temephos has the following properties:

Melting point:	30.0-30.5°C (BCPC, 1977)
Solubility:	in water, 0.0000025% (Metçalf, 1981); soluble in acetonitrile, carbon tetrachloride, diethyl ether, ethylene dichloride, toluene; insoluble in hexane and methylcyclohexane (BCPC, 1977)
Stability:	stable at 25°C; stable in natural fresh and salt water at pH 5-7; undergoes hydrolysis at pH <1 and >9 (BCPC, 1977).

1.3. PRODUCTION DATA

Temephos is produced by the American Cyanamid Company, Agricultural Division, Linden, New Jersey (SRI, 1983). The production volume in 1976 was 1 million pounds/year (Ayers and Johnson, 1976). It is made by reacting O,O-dimethyl phosphorochloridothioate with di-(4-hydroxyphenyl) sulfide, produced from phenol and SCl_2 (BCPC, 1977).

1.4. USE DATA

Temephos is a larvicide used to control mosquitoes, black flies, midges, moths and sand flies, body lice and fleas on dogs and cats. It may also be used on crops to control cutworms, thrips and Lygus bugs (BCPC, 1977).

2. ENVIRONMENTAL FATE AND TRANSPORT

Limited information on the fate and transport of temephos in the environment was available. As a larvicide, temephos enters the aquatic environment directly from application to ponds and lakes that breed insects. The fate of this chemical in the aquatic environment will depend upon its ability to be hydrolyzed, to undergo other chemical and photochemical reactions and to be microbially degraded. As previously mentioned (see Section 1.2.), temephos is stable in natural fresh and salt water with optimum stability at pH 5-7. Hydrolysis occurs at pH <2 and >9 (BCPC, 1977).

Temephos at a concentration of 600 ppm in methanol was 50% degraded by sunlight in 2 days and completely in 6 days (Rosen, 1972). The first degradation product was temephos-sulfoxide, which was further degraded to at least six other products. Temephos-sulfone was also detected, being formed either directly from temephos or from the sulfoxide. It was pointed out that care should be taken in extrapolating these results to environmental conditions, since the experiment was conducted in methanol at a relatively high temephos concentration.

Information regarding microbial degradation of temephos in water was obtained from a study in which a pure culture of a Pseudomonas sp. isolated from sewage water was incubated with ring-^{3}H-temephos (Daorai and Menzer, 1977). As the number of days of incubation increased from 1 to 10, the amount of radioactivity associated with the water soluble, highly polar metabolites increased from 24-42% of the total recovered radioactivity. The majority of radioactivity in the organic extraction layer was unchanged temephos. Metabolites consisted of 2 unknowns along with those indentified as the sulfoxide, the mono-oxon, the mono-oxon sulfone and the monophenol derivatives of temephos. Caution must be exercised in extrapolating data from sewage and pure cultures to environmental conditions.

The U.S. EPA summarized a study from the foreign literature (Drevenkar et al., 1977). Temephos was added as a granular formulation at ~0.7 ppm to a polluted brook or to puddle water, and after 26 days, 40 and 57%, respectively, of the temephos remained, indicative of relatively rapid removal. The water was not analyzed for metabolites.

Henry et al. (1971) added temephos to pond water in beakers to give an initial concentration of 0.1 ppm. The dissipation was measured at temperatures of 10, 25 and 38°C. Within 48 hours, the concentration of temephos in the pond water reached a steady state of 0.02-0.04 ppm with no significant difference observed for the three temperatures. Much of the temephos was found associated with organic matter in the pond water. It was concluded that hydrolysis and oxidation may account for some of the dissipation; however, most of the temephos was adsorbed to organic matter and slowly released to achieve the steady state.

The removal of temephos from water was studied by Hughes et al. (1980). The time for 90% disappearance of temephos applied at 10 ppb to the surface of artificial polyethylene-lined ponds and activated by leaf litter (sediment) was 1.05 days. Ten days were required for a decline of temephos concentration to 0.01 ppb. Adsorption by polyethylene played a significant role in temephos disappearance, with a maximum of 1560 ppb adsorbed in <1 day. The rapid adsorption corresponded to rapid partitioning. This was followed by desorption from polyethylene, such that small amounts of insecticide were rereleased into the aqueous phase and, after a time, equilibrium was reached. Analysis of organic matter for temephos was precluded by technical difficulties; however, significant sorption to and disorption from sediment (less than from polyethylene) was observed for Dursban and Reldan, two related organophosphorus insecticides, and may also apply to temephos.

The behavior of insecticides in artificial ponds did not completely reflect the behavior in natural systems.

The U.S. EPA (1981) summarized the results of a study from the foreign literature (Vrochinskii, 1976). An unspecified formulation of temephos was added to a model reservoir (18-20°C, pH 7.4-8, dissolved oxygen = 6-8 ppm) at an intial concentration of 3.5 ppm. Within 9 days, 50% had dissipated, and by 113 days, only 5% of the initial concentration was detected.

Temephos may also be removed from water through accumulation in aquatic animals. Miles et al. (1976) reported that the bioconcentrations of temephos in bluegills 16 hours after treatment in aquaria with concentrations of 0.0216 and 0.00216 ppm were 125 and 144, respectively. Tsai (1978) reported a bioconcentration factor of ~2 in Indopacific milkfish (Chano chanos) that had been exposed to ~0.35 ppm of a 30% emulsifiable concentrate of temephos. The duration of exposure was unspecified. The level of temephos residue in both whole and edible fish tissue declined from ~0.7 to 0.02 ppm in 14 days.

Information regarding the fate of temephos in soil was unavailable; however, photodegradation may occur at the soil surface and soil microbes may be capable of biodegradation. The only information on transport in soil was obtained from an abstract of a French study (Mestres and Chevallier, 1971). Temephos diffused through waterlogged soil to a depth of 40-50 cm within 3 days of application at an unknown rate. The concentration at this depth and time was approximately that at the soil surface (0.3 mg/kg).

Temephos may enter the atmosphere through volatilization from the water or soil surface. Information regarding chemical reactions were unavailable, but an abstract of a Russian study (Klisenko and Plis'mennaya, 1979) reported a half-time of 186 minutes for the photoxidation of temephos in

air. Experimental details were not given. Removal from the atmosphere may be accomplished by dry deposition on land or water of the insecticide sorbed to particulate matter or by precipitation with rain; however, no information on these processes was available.

3. EXPOSURE

STORET contained monitoring data from only one station. The Roanoke River at Kerr Reservoir and Dam, Virginia, contained 4950 µg/l temephos the week of 8/3/70.

Blinn and Pasarella (1966) detected 2-11 ppb temephos in natural stream water samples and <0.1 ppm in stream bed mud taken from several locations in California and New Jersey. Florida oysters samples contained 0.05-0.14 ppm, samples of California rice grain contained <0.01 to 0.07 ppm and rice foliage contained 0.01 ppm.

4. PHARMACOKINETICS

4.1. ABSORPTION

^{3}H-Temephos was absorbed from the gastrointestinal tract of rats administered the compound by gavage at a dose of ~32 mg/kg in sesame oil (Blinn, 1969). Peak concentrations of radioactivity (~20-25 ppm) in blood, obtained via cardiac puncture of groups of rats sacrificed at intervals, were reached in 5-8 hours and declined with an average half-life of 10 hours. When blood was collected at intervals from the tail vein of a single rat, peak radioactivity (~9 ppm) was reached at about the same time and declined in a similar manner. Increasing the amount of sesame oil as vehicle increased the urine/feces ratio of radioactivity. The investigator suggested that the increased amount of sesame oil enhanced the absorption from the gastrointestinal tract.

Guinea pigs treated by gavage with 32 mg/kg of ^{3}H-temephos achieved a peak concentration of radioactivity in blood of only 0.66 ppm in 8 hours, while bile from the excised gall bladders contained 59.5 ppm of radioactivity, calculated as temephos, in 8 hours (Blinn, 1969).

4.2. DISTRIBUTION

Blinn (1969) also studied the tissue distribution of radioactivity from ring-^{3}H-temephos administered by gavage to rats. After 48 hours of a 5 mg/kg dose, appreciable radioactivity was found only in adipose tissue (1.25 ppm as temephos). After 72 hours of a dose of 6.2 mg/kg ^{3}H-temephos, 1.75 ppm, 0.51 ppm and 0.24 ppm of radioactive residue were found in fat, intestine and stomach, respectively. Other organs examined were liver, kidney and muscle, all of which contained small amounts (<0.19 ppm) of radiolabel calculated as temephos.

In an abstract of a Russian study (Biryukova, 1977), it was reported that in rabbits the greatest amounts of temephos (0.12-0.5 mg/kg tissue) were found in the heart, muscles, liver and kidney following oral administration of the insecticide at a 100 mg/kg dose. No residues were detected after 30 days. Additional details were not given.

4.3. METABOLISM

Blinn (1969) identified the nature of the radioactive residues in rat blood following oral doses of ~32 mg/kg ring-^{3}H-temephos. Unchanged temephos amounted to 24% of the total blood radioactivity after 2 hours and 7% after 48 hours. Water soluble metabolites in rat blood were identified as 4,4'-thiodiphenol and 4,4'-sulfinyldiphenol. Analysis of radioactive compounds in fat revealed only unchanged temephos and temephossulfoxide. The majority of radioactive residues in the 24-hour urine were identified as 4,4'-thiodiphenol, 4,4'-sulfinyldiphenol and 4,4'-sulfonyldiphenol. Additional radiolabeled compounds in urine were sulfate ester conjugates, several unknowns and a trace of unchanged temephos.

In an abstract of a study (Kurtz and Strassman, 1977), it was reported that dimethyl phosphate and dimethyl phosphorothionate were detected in urine samples taken from human populations exposed to temephos that had been used for mosquito control. Further details were not given.

4.4. ELIMINATION

Rats receiving intragastric doses of 5.0 mg/kg of ^{3}H-temephos eliminated 21.1% of the radioactivity in the 24-hour urine and 32.3% of the radioactivity in the 24-hour feces (Blinn, 1969). Elimination was 98% complete in 48 hours, with a total of 33.1% of the administered radioactivity present in urine and 64.9% present in feces. Increasing the dose to 45.8 mg/kg had little effect on the urinary excretion of radioactivity.

In contrast, guinea pigs receiving 31.9 mg/kg of ^{3}H-temephos by gavage eliminated only 6.7% of the administered radioactivity in the urine and 68.9% in the feces (Blinn, 1969). Biliary excretion in guinea pigs was suggested by the relatively high levels of radiolabel present in bile from excised gall bladders (59.5 ppm compared to 0.66 ppm in blood at 8 hours) of treated guinea pigs.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of temephos were not located in the available literature and this chemical is not scheduled for testing by the National Toxicology Program (NTP, 1983).

5.2. MUTAGENICITY

Temephos was non-mutagenic to Salmonella typhimurium strains TA100 and TA98 in the presence or absence of Aroclor-induced mouse liver S-9 enzymes when tested in a plate incorporation assay at a concentration of <1 µmole/plate (Bartsch et al., 1980). Mayberry and Savage (1978) also reported, in abstract form, that temephos was non-mutagenic to S. typhimurium with or without metabolic activation by mammalian microsomes. It was not clear from the abstract in which strains, at what concentrations and by which method of application the compound was tested.

5.3. TERATOGENICITY

Gaines et al. (1967) started 15 pairs of male and female Sherman rats (placed together for breeding) on diets containing 500 ppm temephos (25 mg/kg/day). The dose was continued throughout mating, gestation, birth and weaning. No teratogenic or fetotoxic effects were observed. RBC cholinesterase was inhibited 90% in dams within 48 days of dosing and 30% in 21-day-old weanlings.

In a study reported in abstract form, Angerhofer et al. (1978) found no teratogenic effect of temephos administered to pregnant New Zealand white rabbits on days 6-18 of gestation at an intragastric dose of 32 mg/kg/day or at a dermal dose of 164 mg/kg/day. Maternal RBC chlorinesterase activity was significantly decreased after either treatment, while the dermal application produced unspecified toxic effects in both does and fetuses. Further details were not given in the abstract.

As discussed more fully in Section 5.5. on the effects of long-term exposure to temephos, Palmer (1968) reported that a calf born to a heifer receiving temephos at a dose of 1.3-1.4 mg/kg/day for 1 year was weak and died within 48 hours. Another heifer given temephos in drinking water at a concentration of 10 ppm gave birth to a still-born calf. Both calves had bilateral corneal opacity. Although these fetal effects may have been attributable to maternal exposure to temephos, no calves were born to control heifers for comparison.

McCarty et al. (1968) failed to observed any teratogenic effect in 11 lambs born to ewes exposed to temephos (see Section 5.5. for doses and durations).

5.4. OTHER REPRODUCTIVE EFFECTS

Information regarding reproductive effects of temephos is limited to data of an unpublished study that was summarized by U.S. EPA (1981). McNerney et al. (1968) found no reproductive effects in rats treated with dietary concentrations of 25 or 125 ppm temephos, and no effects in the offspring. Further details of this study were not provided.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The available studies in which temephos was administered repeatedly are mainly concerned with the anticholinesterase effects of the compound.

Gaines et al. (1967), in an extensive investigation of the toxic effects of temephos, administered the insecticide orally to a variety of species at a variety of doses for various durations. Male Sherman rats (10 per group) were given temephos daily in the diet at concentration of 0, 2, 20, 200 and 2000 ppm for 99 days. Based upon measured food intake, the investigators calculated that these concentrations corresponded to the following dose ranges: 0; 0.12-0.24 mg/kg; 1.2-2.4 mg/kg; 11-24 mg/kg; and 150 mg/kg.

respectively. No effects were observed at <20 ppm temephos. RBC cholinesterase activity was 100% inhibited after 2 weeks at 200 ppm temephos. The inhibition was followed by a recovery to 71% inhibition by 99 days. At the 2000 ppm level, 8 rats died and 2 had depressed cholinesterase activity. Gross and histological examination revealed no abnormalities.

In another experiment by these investigators (Gaines et al., 1967), male Sherman rats (7-14 per group) were given temephos in peanut oil by gavage in doses of 0, 1, 10 or 100 mg/kg/day for 44 days. Under these conditions, the 1 mg/kg/day dose represented a no-effect level. At 10 mg/kg/day, RBC cholinester-ase activity was inhibited to 31% of normal within 2 weeks and recovered to 47% of normal by day 44. In rats receiving 100 mg/kg/day, cholinesterase activity was depressed to a greater degree and the rats developed signs of cholinergic poisoning, a typical response to organophosphate compounds.

Murphy and Cheever (1972) adminstered temephos to groups of 5 male Holtzman rats at concentrations of 0, 1, 3 or 5 ppm in the drinking water daily for 8 weeks. These concentrations represent the following doses: 0, 0.5, 0.3, or 0.5 mg/kg, calculated using an average water consumption of 100 ml/kg/day, the midpoint of the range (80-120 ml/kg/day) provided by the investigators. No effect on weight gain or water consumption or on brain, submaxillary, plasma and RBC cholinesterase was observed. Liver carboxylesterase activity was inhibited in what appeared to be a dose-related manner, although values significantly different from controls were observed at only a few sampling times during the experiment.

The results of several unpublished studies in rats have been summarized by U.S. EPA (1981). Rats maintained on a diet containing 6-350 ppm temephos for 90 days had depressed RBC cholinesterase activity (Levinskas,

1965). At the 350 ppm dietary level body weight gain was reduced, but there were no effects on mortality or food consumption and no histopathologic changes to unspecified tissues and organs. In male rats receiving dietary concentrations of temephos at 0, 250, 500 or 1000 ppm for 30 days, no systemic effects were observed at the 250 ppm level, but body weight gain was reduced at 500 ppm temephos (American Cyanamid Co., 1964). Cholinesterase activity was inhibited at all levels. It was stated that RBC, plasma and brain cholinesterases were inhibited, but it was unclear whether all three activities were inhibited at all levels. No adverse effects were observed in Sprague-Dawley rats maintained on diets containing 10, 100 or 300 ppm temephos for 2 years; however, the anticholinesterase effects were not studied (Underwood, 1977). Further details of these studies were not provided.

Rabbits (4 per group) received temephos by gavage in doses of 0, 0.1, 1 or 10 mg/kg/day for 35 days (Gaines et al., 1967). No effects were observed at <1 mg/kg/day. At 10 mg/kg/day, RBC cholinesterase inhibition (26% of normal) and recovery (47%) were observed at 7 and 35 days, respectively. No pathological abnormalities were observed.

Dogs (1 male and 1 female per group) of unspecified breed were given temephos at concentrations of 0, 10 or 50 ppm (0; 0.6-0.8; and 3.4 mg/kg/day, as calculated by the investigators from measured water intake) in drinking water for 129 days (Gaines et al., 1967). No symptoms of poisoning or effect on RBC cholinesterase were observed at the 10 ppm level. The dogs receiving 50 ppm temephos had progressive cholinesterase inhibition (22 and 50% of normal at 129 days for the male and female, respectively).

The U.S. EPA (1981) also summarized an unpublished study in dogs. Temephos was administered in the diet of dogs at concentrations of "700/500

ppm* for 90 days (Hutchinson and Levinskas, 1965). It is unclear from the summary whether the dogs were given 500-700 ppm, or whether an initial concentration of 700 ppm was later lowered to 500 ppm. The treated dogs had reduced RBC, plasma and brain cholinesterase activity. No effects were observed on mortality, food consumption or histopathology in unspecified organs and tissues. Further details were not provided.

Laws et al. (1967) failed to find significant differences in RBC or serum cholinesterase values between human male volunteers who were given daily oral doses of temephos for 4 weeks and controls who drank a formula without temephos. One group of 10 men received 2 mg/man/day in 30 ml of formulated milk, after which the dose was doubled every 3 or 4 days to a maximum dose of 256 mg/man/day. Ten men served as controls. Another group of 8 men were given 64 mg/man/day (0.91 mg/kg/day, assuming 70 kg/man) and 8 men served as controls. No clinical signs of toxicity were observed in any of the treated men.

Two studies were available on the effects of long-term oral exposure to temephos in cattle and sheep (Palmer, 1968; McCarty et al., 1968). Although results in ruminants are difficult to extrapolate to other mammals because of the differences in digestive systems, temephos was shown to have anti-cholinesterase activity in these animals.

A heifer and a steer were given oral doses of 420 mg/animal (1.3-1.4 mg/kg) daily for 1 year. The steer developed conjunctivitis and had increased salivation and shoulder and hip stiffness after 4 months. This was followed by anorexia, swelling and ulceration of the lower extremities and stumbling gait, progressing to periods of prostration and convulsions and weight gain greatly reduced from normal. Serum cholinesterase activity decreased gradually to 37% of pre-exposure values after 9 months and

recovered gradually to 64% after 12 months. The heifer steadily gained weight and gave birth to a fully developed female calf, which had bilateral corneal opacity and died within 48 hours. The only effect in the heifer was a 50% reduction in cholinesterase activity. Administration of temephos to cattle, 2 heifers and 2 steers per group, in concentrations of 0, 10 or 20 ppm in the drinking water for 6 months, did not result in significant differences in serum cholinesterase or weight gain when compared to controls. A dead calf, born to a 10 ppm level heifer, had bilateral corneal opacity.

McCarty et al. (1968) administered temephos to sheep (ewes, rams and wethers) orally in a gelatin capsule in doses of 1.12-5 mg/kg/day or in the drinking water at a concentration of 20 ppm for periods of 157-422 days. No toxic effects were observed for any treatment. Whole blood cholinesterase activity became depressed and then recovered during the treatments.

In an abstract of a Russian study, (Goncharenko, 1975), it was reported that inhalation of 12.9 mg/m³ of temephos vapor for 16 weeks by cats and rats produced swelling of liver and kidney parenchyma and morphological changes in brain neurocytes. Further experimental details were not provided, and the reliability of data from such an abstract is questionable.

5.6. OTHER RELEVANT INFORMATION

NIOSH (1983) lists the following LD_{50} values for temephos:

oral - rat - 1000 mg/kg
oral - mouse - 223 mg/kg
skin - rat - 1370 mg/kg
skin - rabbit - 970 mg/kg

The above values are quite different from those reported by Gaines et al. (1967) listed below:

oral - rat - male - 8600 mg/kg
- female - 13,000 mg/kg
oral - mouse - male - 4700 mg/kg
skin - rat - male and female - >4000 mg/kg.

The survival time for the mice and rats ranged from 1-18 days (Gaines et al., 1967). Discrepancies in LD_{50} values may be due to the use of different strains of animals and different temephos formulations.

In addition to the anticholinesterase effects of temephos in mammals, the insecticide has been found to potentiate the brain anticholinestase activity of malathion (Cohen and Murphy, 1971) and to enhance the lethality of malathion 4-fold (Gaines et al., 1967) in rats.

Other effects of temephos in rats include reduced liver glutamate dehydrogenase and aminopyrine demethylase activities and cytochrome P450 content following intraperitoneal injection of 10 and 300 mg/kg for 10 days (Ennin and Franklin, 1979). Behavioral changes, as evidenced by impairment of a pre-conditioned response to shock avoidance, associated with depressed brain, RBC and plasma cholinesterase activity were observed in rats injected intraperi-toneally with 1000 mg/kg temephos (Kurtz and Weeks, 1979).

Subcutaneous administration of 1000 mg/kg temephos or dietary concentrations >250 ppm temephos resulted in leg weakness and early deaths in hens. Oral doses of 25 mg/kg/day for 5 days were lethal to chicks and ducklings (Gaines et al., 1967).

Temephos induced porphyria in enzyme-induced, but not uninduced, primary liver cell cultures of chick embryos (Koeman et al., 1980).

As reported in an abstract of a Russian study (Mozes, 1977), autopsy data from humans fatally poisoned with temephos showed pulmonary hemorrhaging, edema, decreased cholinesterase levels and pneumonia.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute lethal effects of temephos have been determined for several species of freshwater fish common to the United States (Table 6-1). Testing under static conditions indicates that coho salmon, rainbow trout and lake trout are the most sensitive species tested with technical grade temephos (Johnson and Finley, 1980). These data indicate that formulations of temephos, emulsifiable concentrate (46%) or wettable powder (50%) are more toxic than the technical compound (see Table 6-1). The limited data on flow-through testing of temephos indicate that this method of study enhances temephos toxicity (Johnson and Finley, 1980).

The acute lethality of temephos has also been determined in several freshwater species not common to the United States. Verma et al. (1978) reported 24, 48 and 96-hour LC_{50} values of 217.3, 225.6 and 217.3 mg temephos/ℓ for Channa gachua. The 24, 48, 72 and 96-hour LC_{50} values for the temephos formulation, 500 EC, were 223.9, 215.1, 211.3 and 206.6 mg/ℓ in Saccobranchus fossilis (Verma et al., 1982). The 24 and 48-hour LC_{50} values for temephos in Aplocheilus lineatus and Macropodus cupanus were 1.72 and 1.25, and 11.75 and 11.42 mg/ℓ, respectively (Jacob et al., 1982).

Juvenile striped bass, Morone saxatilis, were tested for toxicity to technical temephos (90% purity) under marine conditions (Korn and Earnest, 1974). The 96-hour LC_{50} value, determined during intermittent flow testing, was 1.0 mg/ℓ.

The oral LD_{50} of temephos, administered by gelatin capsule, in adult bullfrogs was determined to be >2000 mg/kg (Tucker and Crabtree, 1970). The LC_{50} values for temephos in Rana chensinensis and Hynobius retardatus were 4.18 and 3.97 mg/ℓ, respectively (Hattori, 1974).

TABLE 6-1

Acute Lethal Effects of Temephos to Freshwater Fish

Species	Duration (hr)	Concentration (mg/L)	Method	Effect	Reference
Rainbow trout, Salmo gairdneri	96	3.49[a]	static	LC_{50}	Johnson and Finley, 1980
Rainbow trout, Salmo gairdneri	96	0.16[b]	static	LC_{50}	Johnson and Finley, 1980
Atlantic salmon, Salmo salar	96	21.0[a]	static	LC_{50}	Johnson and Finley, 1980
Atlantic salmon, Salmo salar	96	6.7[c]	static	LC_{50}	Johnson and Finley, 1980
Brook trout, Salvelinus fontinalis	96	12.8[a]	static	LC_{50}	Johnson and Finley, 1980
Brook trout, Salvelinus fontinalis	96	5.0[c]	static	LC_{50}	Johnson and Finley, 1980
Brook trout, Salvelinus fontinalis	48	1.50	static	LC_{50}	FWPCA, 1968
Lake trout, Salvelinus namaycush	96	3.65[a]	static	LC_{50}	Johnson and Finley, 1980
Lake trout, Salvelinus namaycush	96	1.05	flow-through	LC_{50}	Johnson and Finley, 1980
Fathead minnow, Pimephales promelas	96	34.1[a]	static	LC_{50}	Johnson and Finley, 1980
Channel catfish, Ictalurus punctatus	96	>10.0[a]	static	LC_{50}	Johnson and Finley, 1980
Channel catfish, Ictalurus punctatus	96	3.23[b]	static	LC_{50}	Johnson and Finley, 1980
Bluegill sunfish, Lepomis macrochirus	96	21.0[a]	static	LC_{50}	Johnson and Finley, 1980
Bluegill sunfish, Lepomis macrochirus	96	1.14[b]	static	LC_{50}	Johnson and Finley, 1980
Coho salmon, Oncorhynchus kisutch	96	0.35[b]	static	LC_{50}	Johnson and Finley, 1980
Largemouth bass, Micropterus salmoides	96	1.44[b]	static	LC_{50}	Johnson and Finley, 1980
Cutthroat trout, Salmo clarki	96	0.20	flow-through	LC_{50}	Johnson and Finley, 1980
Carp, Cyprinus carpio	1	5.0	static	50% mortality	Walls et al., 1967
Mosquitofish, Gambusia affinis	48	5.0	NR	no mortality	Barnasch and Walls, 1974

[a]Technical temephos (86-90%)
[b]Emulsifiable concentrate (40%)
[c]Wettable powder (50%)
NR- Not reported

05439
05/23/84

The acute lethality of temephos has been determined on several non-target species of aquatic invertebrates (Table 6-2). Stonefly larvae and scuds had LC_{50} values below 1.0 mg/ℓ (Sanders, 1969; Sanders and Cope, 1968; Johnson and Finley, 1980). Blackfly larvae, Simulium sp., (the target species of temephos spraying) had 24-hour LC_{50} values <0.02 mg/ℓ (Mohsen and Mulla, 1981). As noted in toxicity testing with fish, intermittent flow decreased the 96-hour LC_{50} value in Korean shrimp from 2.55 (in static tests) to 0.25 mg/ℓ (U.S. EPA, 1972). Temephos had little effect on the mortality of oysters, Crossostrea virginica, exposed at 1 and 10 mg/ℓ for up to 99 days (Tripp, 1974). During field studies on the populations of aquatic crustaceans (Frank and Sjogren, 1978) and salt marsh snails, Melampus bidentatus (Fitzpatrick and Sutherland, 1978), after mosquito control spraying with temephos, both research teams reported no toxic effects on the species tested. Temephos was applied at 0.025 (Frank and Sjogren, 1978) and 0.1 pound/acre (Fitzpatrick and Sutherland, 1978).

In vivo exposure of killifish, Fundulus heteroclitus, to temephos decreased brain acetylcholinesterase activity, AChE, in a dose-related fashion (Thirugnanam and Forgash, 1975). In vitro studies with isolated brain extracts from F. heteroclitus showed temephos to be non-inhibitory on AChE, but temephos metabolites did inhibit AChE activity.

6.2. CHRONIC EFFECTS

The effects of temephos at 0.25, 0.5, 1.0 and 1.5 mg/ℓ on the reproduction, egg production and survival of juvenile stages were studied in guppies, Poecilia reticulata (Yasuno et al., 1980). Fish were allowed to acclimatize for a 4-month pre-exposure period during which time reproduction was studied. Temephos prepared as an emulsion was administered for a 2-month period (one-half the 60 ℓtest volume was replenished daily with an

TABLE 6-2

Acute Lethal Effects of Temephos to Aquatic Invertebrates

Species	Duration (hr)	Concentration (mg/l)	Method	Effect	Reference
Scud, Gammarus lacustris	96	0.08	static	LC_{50}	Johnson and Finley, 1980
Scud, G. lacustris	48	0.64	static	LC_{50}	FWPCA, 1968
Scud, G. lacustris	24	0.96	static	LC_{50}	Sanders, 1969
	48	0.64	static	LC_{50}	Sanders, 1969
	96	0.08	static	LC_{50}	Sanders, 1969
Korean shrimp, Palaemon macrodactylus	96	2.55	static	LC_{50}	U.S. EPA, 1972
	96	0.25	intermittent-flow	LC_{50}	
Stonefly larvae, Pteronarcys californica	48	0.10	static	LC_{50}	FWPCA, 1968
Stonefly larvae, Pteronarcys californica	96	0.01	static	LC_{50}	Johnson and Finley, 1980
Stonefly larvae, Pteronarcella badia	96	0.03	static	LC_{50}	Johnson and Finley, 1980
Stonefly naiads, Pteronarcys californica	24	0.12	static	LC_{50}	Sanders and Cope, 1968
	48	0.10	static	LC_{50}	
	96	0.01	static	LC_{50}	
Blackfly larvae, Simulium arcus	24	0.02	static, 60-minute exposure	LC_{50}	Mohsen and Nalla, 1981
Blackfly larvae, S. virgatum	24	0.008	static, 60-minute exposure	LC_{50}	Mohsen and Nalla, 1981
Aquatic insect, Baetis parvus	24	0.01	static, 60-minute exposure	LC_{50}	Mohsen and Nalla, 1981
Aquatic insect, Hydropsyche californica	24	1.3	static, 60-minute exposure	LC_{50}	Mohsen and Nalla, 1981

05/23/84

appropriate concentration of pesticide) and an extended 2-month observation period was allowed thereafter. Mortality among adults exposed at 1.5 mg temephos/ℓ was noted. The number of live juveniles was decreased in fish treated at 1.5 mg/ℓ. This effect was noted after 1 month of exposure and was evident during the 2 months post-exposure. Premature births of various staged embryos were noted in groups exposed at 1.0 and 1.5 mg temephos/ℓ (Yasuno et al., 1980). Survival of fry was not different among treated groups or controls.

The effects of temephos on a tropical African trout, Sarotherodon mossambicus, were determined during 10 weeks of exposure (Adeney and Matthiessen, 1979). Temephos concentrate (696 mg/ℓ) was applied daily at 10 mℓ/day to give a final nominal concentration of 0.05 mg active ingredient/ℓ. During the exposure period, growth of S. mossambicus in both length and weight was not significantly different from controls. Reproduction occurred and viable broods of fry were produced during the exposure period.

The hatching success of the amphibians, Rana chensinensis and Hynobius retardatus, was not affected by 1 mg temephos/ℓ (Hattori, 1974).

6.3. PLANT EFFECTS

Birmingham and Colman (1977) determined the effect of temephos at 0.001, 0.01, and 0.1 mg/ℓ on the growth of seven species of freshwater algae. No significant effect on growth was noted in the green algae, Chlorella pyrenoidosa and Chlamydomonas reinhardii, the blue-green algae, Coccochloris peniocystis, Anabaena flos-aquae (nitrogen-rich media) and Oscillatoria sp., and the diatom, Navicula minima, at any concentration tested when compared to untreated controls. The blue-green algae, A. flos-aquae, grown on nitrogen-free medium showed a significant ($p<0.05$) increase in growth when

exposed at 0.01 and 0.1 mg temephos/L (Birmingham and Colman, 1977). Navicula pelliculosa showed a significant ($p<0.05$) decrease in growth after treatment at 0.01 mg temephos/L, but not at the higher or lower temephos concentration. In studies with Chlorella vulgaris, Low-Goh et al. (1981) reported that temephos at 0.5, 1.0 and 4.0 mg temephos/L seemed to slightly reduce cell duplication. At 10.0 and 40.0 mg temephos/L, C. vulgaris growth was completely halted (100% lethality) (Low-Goh et al., 1981).

The effect of temephos on the growth of four species of marine phytoplankton, Dunaliello euchlora, Phaeodactylum tricornutum, Skeletonema costatum and Cyclotella nana, was determined by Derby and Ruber (1970). Exposure was for 24 hours at 0.01, 0.1 and 1.0 mg temephos/L. A significant ($p<0.05$) dose-related reduction in growth was reported in D. euchlora, P. tricornutum and S. costatum exposed at 0.1 and 1.0 mg/L. Cyclotella nana showed a significant ($p<0.05$) growth reduction (80%) only at 1.0 mg temephos/L (Derby and Ruber, 1970). Maly and Ruber (1983) reported that temephos at 10.0 mg/L for 48 hours of exposure significantly ($p<0.05$) reduced the growth rate of the marine diatom, Amphiprora sp. Two species of diatom, Nitzschia closterium and Amphora coffeaformis borealis, a green algae, Chlorococcum sp., and a dinoflagellate, Gonyaulax sp., were not affected at 10.0 mg temephos/L for 48 hours (Maly and Ruber, 1983).

6.4. RESIDUES

Pertinent data regarding the occurrence and persistence of temephos residues in aquatic organisms or the aquatic environment were not located in the available literature.

6.5. OTHER RELEVANT INFORMATION

Additional data pertinent to the aquatic toxicity of temephos were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The American Conference of Governmental Industrial Hygienists (ACGIH, 1982) has adopted a TWA-TLV of 10 mg/m³ and a STEL of 20 mg/m³ for temephos.

A tolerance of 0.1 ppm was established by the U.S. EPA for combined negligible residues of temephos and its sulfinyl metabolite in or on raw agricultural commodities and citrus fruit (Federal Register, 1972). In the U.S.S.R., the maximum permissible level for human exposure to inhalation of temephos is 0.5 mg/m³ (Goncharenko, 1975) and the maximum permissible concentration of temephos in reservoir water was recommended as 1 mg/l (Akhundov et al., 1976).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of temephos were not located in the available literature.

8. RISK ASSESSEMENT

No data were available on the carcinogenic potential of temephos. Results of mutagenicity testing of the insecticide in S. typhimurium with or without metabolic activation were negative (Bartsch et al., 1980; Mayberry and Savage, 1978). Temephos was not teratogenic to rats (Gaines et al., 1967), rabbits (Angerhofer et al., 1978) or sheep (McCarty et al., 1968). It is difficult to attribute the bilateral corneal opacity and early deaths of 2 calves born to heifers exposed to temephos to the exposure (Palmer, 1968) because the number of animals was small and no calves were born to the unexposed control heifers for comparison.

Studies on the effects of long-term oral exposure to temephos in laboratory animals are summarized in Table 8-1. Rats exposed to dietary concentrations of 200 ppm (corresponding to 11-24 mg/kg bw/day) for 99 days had 100% inhibition of RBC cholinesterase activity without any apparent toxicity or pathologcial effects (Gaines et al., 1967). This level appears to be a NOAEL. At doses of 100 mg/kg bw/day for 44 days, there were signs of cholinergic poisoning. Inhibition of RBC cholinesterase also occurred in rats treated with 10 mg/kg bw/day temephos and in rabbits treated with 1 mg/kg bw/day temephos by gavage, and in dogs exposed to 50 ppm temephos in drinking water (3.4 mg/kg bw/day). This effect was found in cattle (Palmer, 1968) and sheep (McCarty et al., 1968) at low doses ($\leq$5 mg/kg bw/day).

The unpublished studies summarized by U.S. EPA (1981) are not included in Table 8-1. The summaries provide inadequate detail to influence the risk assessment, although the results tend to support the NOAEL of 200 ppm temephos in the diet. RBC cholinesterase activity was inhibited in rats receiving 250 ppm temephos in the diet for 90 days (Levinskas, 1965). At 350 ppm, the rats had reduced body weight gain. Rats treated with temephos

TABLE 8-1

Summary of Oral Subchronic Studies on Temephos Toxicity to Laboratory Animals

Species	Number and Sex of Animals	Vehicle	Concentration and/or Dose (ppm, mg/kg)	Duration of Treatment	Effects	Reference
Rat	10 males/group	diet	0, 0 2, 0.12-0.24 20, 1.2-2.4 200, 11-24 2000, 150	99 days	none none none 100% inhibition of rbc cholinesterase in 2 weeks, followed by recovery-8 deaths; inhibition of cholinesterase	Gaines et al., 1967
Rat	7-14 males/group	gavage, in peanut oil	0 1 10 100	44 days	none none 31% inhibition of rbc cholinesterase in 2 weeks, followed by recovery. Greater degree of rbc cholinesterase inhibition; signs of cholinergic poisoning	Gaines et al., 1967
Rat	5 males/group	drinking water	0, 0 1, 0.1 3, 0.3 5, 0.5	56 days	none Depression of liver carboxylesterase activity that appeared to be dose-related. No inhibition of brain, rbc or plasma cholinesterase at any dose.	Murphy and Cheever, 1972
Rabbit	3-4 males/group	gavage, in peanut oil	0 0.1 1 10	35 days	none none none 26% inhibition of rbc cholinesterase in 7 days; 47% inhibition in 35 days.	Gaines et al., 1967
Dog	1 male, 1 female/group	drinking water	0, 0 10, 0.6-0.8 50, 3.4	129 days	none none Progressive inhibition of rbc cholinesterase (22% in males, 50% in females)	Gaines et al., 1967

at concentrations up to 300 ppm in the diet for 2 years had no adverse effects, but the investigators did not measure cholinesterase activity (Underwood, 1977).

Thus, a dose of 17.5 mg/kg bw/day (the midpoint of the 11-24 mg/kg bw/day range calculted for a 200 ppm dietary concentration) of temephos in rats (Gaines et al., 1967) can be considered the NOAEL. Inhibition of RBC cholinesterase without accompanying cholinergic symptoms is not considered an adverse effect, and the inhibition of brain cholinesterase, which was not investigated at this doseage, is considered to have more functional significance (Wills, 1972). An uncertainty factor of 1000 is appropriate for the calculation of an ADI for humans from these subchronic animal data and results in an ADI value of 0.0175 mg/kg bw/day or 1.225 mg/day for a 70 kg man.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews unpublished chronic and subchronic animal data and presents a more detailed summary of the study by Levinskas (1965) than did the U.S. EPA (1981). These additional data indicate that a more conservative ADI should be adopted. An ADI of 0.0054 mg/kg bw/day, or 0.378 mg/day for a 70 kg man was derived based on a dietary NOAEL of 6 ppm (0.54 mg/kg bw/day as determined by the investigator) for RBC cholinesterase inhibition in rats in the 90-day study of Levinskas (1965) and using an uncertainty factor of 100. In consideration of the absence of

outward signs of toxicity, effects on hematologic and biochemical parameters, or other histologic evidence of treatment-releated damage, and since the degree of cholinesterase inhibition would not abe expected to increase substantially with the durationos of exposure >90 days at a given dosage level, this uncertainty factor (10 to account for interspecies extrapolation and 10 for protection of unusually sensitive individuals within the human population) is believed to be appropriate. The dietary level of 18 ppm in the same study was the LOAEL for brain cholinesterase inhibition.

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APPENDIX I:
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in July and August, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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